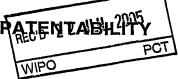
PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTAL LITY (Chapter II of the Patent Cooperation Treats)

(Chapter II of the Patent Cooperation Treaty)



(PCT Article 36 and Rule 70)

Applicant's or agent's file reference									
4239-67618-03	FOR FURTHER AC	FOR FURTHER ACTION See Form PCT/IPEA/416							
International application No. PCT/US2004/022232	International filing date ((day/month/year)	Priority date (day/month/year) 09.07.2003						
	International Patent Classification (IPC) or national classification and IPC A61K33/00, A61P9/08, A61P9/10, A61P9/12								
Applicant THE GOVERNMENT OF THE UNITED STATES OF AMERICA et									
 This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 									
2. This REPORT consists of a tot		=	30.						
3. This report is also accompanie									
i	nd to the International Bure	_	to an fallacia.						
and/or sneets conta	Sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).								
sheets which super beyond the disclos Supplemental Box.	beyond the disclosure in the international application as filed as indicated in them 4 of Roy No. 1 and the								
sequence listing and/or	b. (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)), containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental								
Box Relating to Sequer	nce Listing (see Section 80	2 of the Administrativ	e Instructions).						
4. This report contains indication	s relating to the following i	tems:							
☐ Box No. I Basis of the	opinion		·						
☑ Box No. II Priority	.,								
Box No. III Non-establis	shment of opinion with rega	ard to novelty, inventiv	e step and industrial applicability						
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	tatement under Article 35(citations and explanations	2) with regard to nove s supporting such stat	ity, inventive step or industrial ement						
☐ Box No. VI Certain docu									
☐ Box No. VII Certain defe	cts in the international app	lication							
Box No. VIII Certain observations on the international application									
Date of submission of the demand		Date of completion of	this report						
06.05.2005		22.07.2005							
Name and mailing address of the International preliminary examining authority:	ational	Authorized Officer							
European Patent Office -	Gitschiner Str. 103		The state of the s						
D-10958 Berlin Tel. +49 30 25901 - 0		Siatou, E	in oll jane						
Fax: +49 30 25901 - 840		Telephone No. +49 3	0 25901-327						
		1	- Other our						

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/US2004/022232

_	Box No. I Basis of the report						
1.	With regard to the language , this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.						
	This report is based on translations from the original language into the following language, which is the language of a translation furnished for the purposes of:						
	 □ international search (under Rules 12.3 and 23.1(b)) □ publication of the international application (under Rule 12.4) □ international preliminary examination (under Rules 55.2 and/or 55.3) 						
2.	nave been lumismed to the tece	lith regard to the elements* of the international application, this report is based on <i>(replacement sheets which ave been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this eport as "originally filed" and are not annexed to this report):</i>					
	Description, Pages						
	1-60	as originally filed					
	Claims, Numbers						
	1-15	received on 09.05.2005 with letter of 04.05.2005					
	Drawings, Sheets						
	1/15-15/15	as originally filed					
	☐ a sequence listing and/or ar	ny related table(s) - see Supplemental Box Relating to Sequence Listing					
3.	The amendments have resulted in the cancellation of: the description, pages the claims, Nos. the drawings, sheets/figs the sequence listing (specify): any table(s) related to sequence listing (specify):						
4.	☐ This report has been estable had not been made, since they supplemental Box (Rule 70.2(c))☐ the description, pages☐ the claims, Nos.☐ the drawings, sheets/figs☐ the sequence listing (spical any table(s) related to se	s ecify):					
	* If item 4 applies. so	ome or all of these sheets may be marked "surrounded" "					

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/US2004/022232

_	- Pa	n No U 5	\\.				
_			Priority				
1.		This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:					
		□ copy c	of the earlier application	n wh	ose priority has been claimed (Rule 66.7(a)).		
		□ transla	ation of the earlier appl	icati	on whose priority has been claimed (Rule 66.7(b)).		
2.							
3.	Add	ditional obs	ervations, if necessary	/ :			
	see	separate	sheet				
		•					
		x No. III I olicability	Non-establishment o	f opi	inion with regard to novelty, inventive step and industrial		
1	The	Guantiana	b.a.th.ath				
١.	obv	ne questions whether the claimed invention appears to be novel, to involve an inventive step (to be non- ovious), or to be industrially applicable have not been examined in respect of:					
		the entire international application,					
	\boxtimes	claims Nos. 1-15 in respect of la					
		because:					
	⊠	the said international application, or the said claims Nos. 1-15 in respect of IA relate to the following subject matter which does not require an international preliminary examination (specify):					
			rate sheet				
		the description, claims or drawings (indicate particular elements below) or said claims Nos. are so unclear that no meaningful opinion could be formed (specify):					
		the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.					
		no international search report has been established for the said claims Nos.					
		the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:					
		the writter	n form		has not been furnished		
					does not comply with the standard		
		the comp	uter readable form		has not been furnished		
					does not comply with the standard		
		, with the standard					
		See sepa	rate sheet for further c	letail	is		

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)

Yes: Claims

1-15

No: Claims

Inventive step (IS)

Yes: Claims

1-15

No: Claims

Industrial applicability (IA)

Yes: Claims No: Claims

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item I

Amended claim 1 is allowable.

Re Item III.

Claims 1-15 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

Reference is made to the following documents:

D1: WO 01/89572 A

D2: PNAS, vol. 98, no. 22, Oct. 23 2001, pages 12814-12819 (& T. Lauer et al)

The document **D1** is regarded as being the closest prior art to the subject-matter of claim 1, and shows (the references in parentheses applying to this document):

The use of sodium nitrite for topical application (cf. claims 1-35). Apart from topical treatment, other modes of application (cf. page 12, line 20- page 13, line 11) such as aural, nasal, vaginal, rectal or injectable, depending on the disease to be treated, are also mentioned. Of the diseases to be treated pulmonary hypertension (cf. page 3, lines 5-26) is mentioned.

The subject-matter of claim 1 differs from this known uses in that **non-acidified** sodium nitrite is used.

The subject-matter of claim 1 is therefore new (Article 33(2) PCT).

The problem to be solved by the present invention may be regarded as providing alternative compositions for cardiovascular treatment.

The solution to this problem proposed in claim 1 of the present application, namely the use of non-acidified sodium nitrite, is considered as involving an inventive step (Article 33(3) PCT), for the following reasons.

Unlike **D1**, where the presence of an acid is required in order for the nitric oxide to be released, the present application does not require acidification of the sodium nitrite. In

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

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addition, document **D2**, which was cited by the applicant in the description, states (cf. page 12818, right-hand column, paragraph titled "Nitrite as delivery source of Intravascular NO") that intraarterial infusion of nitrite showed a complete lack of vasodilator action.

Claims 2-15 are dependent on claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step.

For the assessment of the present claims 1-15 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

³rinted: 19/05/2005

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CLAIMS

- 1. A method for treating or ameliorating a condition selected from:
- (a) hepatic or cardiac or brain ischemia-reperfusion injury;
- (b) pulmonary hypertension; or
 - (c) cerebral artery vasospasm,

in a subject by decreasing blood pressure and/or increasing vasodilation in the subject, the method comprising administering non-acidified sodium nitrite to the subject to decrease the blood pressure and/or increase vasodilation in the subject, thereby treating or ameliorating the condition.

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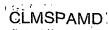
- 2. The method of claim 1, which is a method for treating or ameliorating hepatic or cardiac or brain ischemia-reperfusion injury.
- 3. The method of claim 2, wherein administering sodium nitrite to the subject is intravenous.
 - 4. The method of claim 2 or 3, wherein the sodium nitrite is administered to a circulating concentration of about 0.6 to 240 μ M.
- The method of claim 1, which is a method for treating or ameliorating pulmonary hypertension.
 - 6. The method of claim 5, wherein the pulmonary hypertension is neonatal pulmonary hypertension.

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- 7. The method of claim 5 or 6, wherein administering sodium nitrite to the subject is by inhalation.
 - 8. The method of claim 7, wherein the sodium nitrite is nebulized.

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- 9. The method of any one of claims 5 through 8, wherein the sodium nitrite is administered at a rate of 270 μ mol/minute.
- 10. The method of claim 1, which is a method for treating or ameliorating cerebral artery vasospasm.
 - 11. The method of claim 10, wherein administering sodium nitrite to the subject is intravenous.



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- 12. The method of claim 10 or 11, wherein the sodium nitrite is administered at a rate of about 45 to 60 mg/kg.
- 13. The method of any one of claims 1-12, wherein the sodium nitrite is administered in combination with at least one additional agent.
 - 14. The method of any one of claims 1-13, wherein the subject is a mammal.
 - 15. The method of any one of claims 14, wherein the subject is a human.

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